IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	PICKAR, J., DEY M.
SERIAL NO.	:	09/808,878
FILING DATE	:	March 15, 2001
FOR	:	HORMONE REPLACEMENT THERAPY
EXAMINER	:	Shengjun Wang
GROUP ART UNIT	:	1617

Commissioner for Patents
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APPEAL BRIEF

Appellants respectfully submit this Appeal Brief pursuant to 37 C.F.R. § 1.192 in support of their appeal from the final rejection in this application. Applicants also submit herewith a Request for Extension of Time extending the period for response from September 19, 2004 to October 19, 2004, and the authorization for the Commissioner to charge the required fees. Applicants wish to note that they filed a Request for Oral Hearing on Appeal on April 29, 2004, requesting an oral hearing in connection with this Appeal.

Real Party in Interest

The real party in interest is the assignee of record, Wyeth.

Related Appeals and Interferences

There are no other appeals or interferences known to the Appellants, or to the Assignee or the Assignee's legal representatives involved in the prosecution of this application that will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

Status of Claims

Application serial no. 09/808,878 was originally filed with 68 claims. During prosecution, claims 1-6 and 15-68 were withdrawn in response to a restriction requirement. Claim 69 was added. Subsequently, claims 8-10 and 13-14 were canceled, and claims 7, 11, 12, and 69 were amended. Claims 7, 11, 12, and 69 are pending and stand rejected under 35 U.S.C. §103(a). Appellants appeal the rejection of all pending claims. The appealed claims are reproduced in Appendix A of this brief.

Status of Amendments

No amendments were filed subsequent to final rejection.

Summary of Invention

The present invention relates to a method of treating or inhibiting vasomotor symptoms ("hot flushes") in perimenopausal, menopausal, or postmenopausal women by administering a low dose hormone replacement therapy (HRT) regimen. The claimed low dose HRT regimen comprises a daily dose of conjugated equine estrogens (CEE) of between about 0.3 mg and about 0.45 mg in combination with a daily dose of about 1.5 mg medroxyprogesterone acetate (MPA).

As described in the background section of the pending application, menopause is characterized by the cessation of ovarian function, leading to a substantial decrease in estrogen circulating in the bloodstream. As estrogen levels decline during the time preceding (perimenopause) and following menopause (postmenopause), various physiological changes may result. One such change is vasomotor instability manifested as hot flushes. (*See* paragraphs [0003] - [0004]). Estrogen replacement therapy (ERT) has proven beneficial in providing relief from hot flushes and other physiological changes associated with menopause. (*See* paragraph [0005]). Although ERT reduces the relative risk for ischemic heart disease and osteoporosis, the relative risk of endometrial cancer for postmenopausal women with a uterus may be increased. The addition of a progestin to estrogen therapy prevents estrogen-induced endometrial proliferation. Continuous combined hormone replacement therapy, with appropriate doses of daily estrogen and progestin, has been shown to be effective in

relieving hot flushes and reducing the risk of endometrial cancer. (*See* paragraph [0006]).

Appellants have found that the claimed daily low dose regimen (comprising about 0.3 mg to about 0.45 mg of CEE plus 1.5 mg of MPA) is unexpectedly as effective at reducing hot flushes as the commonly prescribed higher dose regimen. (*See* Lobo Declaration ¶¶ 14 and 15). Moreover, the Appellants' low dose regimen may be advantageous to minimize the occurrence of estrogen-related side effects. (*See* paragraph [0006]). The prior art does not teach or suggest the continuous and uninterrupted administration of a daily low dose regimen comprising about 0.3 mg to about 0.45 mg of CEE in combination with 1.5 mg of MPA.

Issues

1) Whether claims 7, 11, 12, and 69 of the pending application, which stand rejected under 35 U.S.C. § 103(a), are patentable over U.S. Pat. No. 4,826,831 (Re 36,247) to Plunkett (referred to herein as "Plunkett")?

Grouping of the Claims

The pending claims are addressed collectively.

Argument

1. Summary of Argument

In the final Office Action mailed September 10, 2003 (hereinafter "Office Action"), the Examiner rejected claims 7, 11, 12 and 69 of the present application under 35 U.S.C. § 103(a) as being unpatentable over Plunkett. The pending claims of the present application are directed to the continuous and uninterrupted administration of a daily dosage of about 1.5 mg MPA in combination with a dosage between about 0.3 and about 0.45 mg CEE, USP. Plunkett lists a myriad of combinations of various estrogens and progestins in a variety of dosage ranges, in both cyclic and continuous regimens. However, Plunkett does not teach or suggest to one skilled in the art to select the combination of 1.5 mg MPA and about 0.3 to about 0.45 mg CEE for relief of vasomotor symptoms of menopause. Moreover, Plunkett does not describe or suggest a daily dosage of about 1.5 mg MPA at all, much less in combination with the claimed dosage of CEE.

In rejecting the claims under 35 U.S.C. § 103(a), the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). To establish *prima facie* obviousness, the prior art must teach or suggest all limitations of a claimed invention. See MPEP § 2143.03 and *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Appellants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness because Plunkett does not teach or suggest the selection of about 1.5 mg MPA in combination with about 0.3 to about 0.45 mg CEE for the treatment of vasomotor symptoms. Of the myriad of possibilities within the disclosed genus, Plunkett selects a preferred dose of 2.5 mg of MPA and a preferred dose of 0.600 mg CEE – dosages that are far higher than the 1.5 mg of MPA and the about 0.3 to about 0.45 mg of CEE claimed in the present invention. The evidence of record demonstrates that one skilled in the art would not have been motivated to employ lower dosage with any reasonable expectation of success. The record evidence also demonstrates that Plunkett does not suggest the specific combination of Appellants' invention.

Furthermore, Appellants have demonstrated that the present invention achieves unexpected results in comparison to the closest prior art. In addition to the data provided in the specification, the Appellants submitted two declarations under 37 C.F.R. § 1.132 by Rogerio A. Lobo, M.D., a Professor of Obstetrics & Gynecology at the Department of Obstetrics and Gynecology at Columbia University, in support of their showing of unexpected results of the claimed invention over Plunkett. (Declaration under 37 C.F.R. §1.132, dated April 1, 2003, attached as Exhibit 1; and Second Declaration under 37 C.F.R. §1.132, dated December 15, 2003, attached as Exhibit 2). The unrefuted declarations of Dr. Lobo establish that the standard daily regimen of 0.625 mg CEE in plus 2.5 mg MPA was considered the minimum effective dosage for relieving vasomotor symptoms. Appellants have demonstrated that the claimed low dose regimen unexpectedly is equally effective at relieving hot flushes. (See Lobo Declaration ¶ 14 and Second Lobo Declaration ¶ 5). Moreover, since the closest species disclosed by Plunkett (0.6 mg CEE plus 2.5 mg MPA) is clinically equivalent to the higher standard dosage, Applicants' demonstration of unexpected results is equally applicable over the Plunkett regimen.

2. Plunkett

Plunkett, the sole reference cited against Appellants' claims, is directed to a broad genus of HRT. In describing estrogen/progestin combination therapy, Plunkett discloses a plethora of estrogens and progestins that can be combined to treat numerous disorders. Specifically, the following *twenty* estrogens are described as being useful in the estrogen plus progestin combination for treating menopausal or post menopausal disorders: estradiol, estradiol-17beta, estradiol valerate, conjugated equine estrogens, estrene, piperazine estrone sulfate, estriol, estriol succinate, polyestriol phosphate, ethinyl estradiol, mestranol, quinestrol, stilbestrol, stilbestrol dipropionate, diethylstilbestrol, chlorotrianiscos, benzoestrol, hexoestrol, and methallenstril. (Plunkett, Table 1A).

Table 1B of Plunkett specifically discloses the following *seventeen* progestins that may be useful in the continuous HRT regimens: levo-norgestrel, dl-norgestrel, norethindrone, norethindrone acetate, dydrogesterone, medroxyprogesterone acetate, norethynodrel, allylestrenol, lynoestrenol, quingestanol, medrogestone, norgestrienone, dimentisterone, ethisterone, cyproterone acetate, chlormadinone acetate, and magestrol acetate.

Tables 1A and 1B of Plunkett also provide ranges of dosage minimums and maximums, and preferred dosages for the estrogens and progestins listed. For conjugated equine estrogen, Plunkett lists the minimum dosage as 0.3 mg, the maximum dosage as 2.5 mg, and 0.6 mg as the preferred dosage. For medroxyprogesterone acetate, Plunkett provides the minimum dosage as 1 mg, the maximum dosage as 15 mg, and the preferred dosage as 2.5 mg. Plunkett further provides that "[a]ny of the suitable estrogens and progestogens (particularly those listed in the foregoing tables) may be combined with one another in the quantities recited to give estrogen/progestogen combinations within the purview of the invention." (Col. 6, lines 46-50).

Plunkett also provides a list of *twenty* "especially preferred" combinations of estrogen and progestins, only one of which is conjugated equine estrogen with medroxyprogesterone acetate. (col. 6, line 53 - col. 7, line 10). Furthermore, of the thousands of possible combinations of estrogens and progestins, Plunkett only provides data for a single combination in which a study was conducted using a daily regimen of 1 mg 17beta-estradiol plus 75 μg dl-norgestrel. Plunkett does not provide

any data for any combinations of conjugated estrogens in combination with medroxyprogesterone acetate.

3. The Claimed Invention is Not Obvious in View of Plunkett

a) The Relevant Legal Standards

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. *See* MPEP §2142. To establish a *prima facie* case of obviousness, the following three criteria must be met: (1) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art must teach or suggest all elements of the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); and *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Furthermore, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

A claim is considered obvious under 35 U.S.C. §103 if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. §103. The Supreme Court has set forth the following four so-called *Graham* factors to be considered when determining obviousness: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any secondary indicia of nonobviousness. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1996).

Thus, the obviousness test is not only three elements of primary consideration (scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art), but also evidence of secondary considerations when such evidence is present. *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573, 1575 (Fed. Cir. 1984), *cert. denied*, 471 U.S. 1065 (1985). Secondary considerations include unexpected results, commercial

success of the invention, whether the invention solved a long felt need, copying the invention by others in the field, and failure of others to solve the problem that the inventor solved. When unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared to the closest prior art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

b) Plunkett Does Not Teach or Suggest Appellants' Claimed Invention

Appellants respectfully submit that the Examiner has not met her burden of establishing a *prima facie* case of obviousness. Plunkett does not teach each and every element of the claimed invention, and does not provide any suggestion or motivation to use the claimed lower dosage amount of CEE and MPA. (*See* Lobo Declaration ¶17-20). Moreover, at the time of the invention, one of ordinary skill in the art would not have had any reasonable expectation of success by using a lower dosage regimen. As described by Dr. Lobo, the unexpected results showing that a regimen of 1.5 mg MPA in combination with about 0.3 mg to about 0.45 mg CEE reduced the number and severity of hot flushes were contrary to what would have been expected by those skilled in the art. (*See* Lobo Declaration ¶6).

In considering the broad disclosure of Plunkett, one skilled in the art would have to perform undue experimentation to arrive at Appellants' particular low dose combination among the vast possibilities contemplated by Plunkett. Obviousness can only be established if the prior art and/or the knowledge generally available to one of ordinary skill in the art explicitly or implicitly teaches, suggests or motivates those skilled in the art to produce the claimed invention. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). *See also In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). Appellants respectfully submit that neither Plunkett nor the knowledge generally available to those skilled in the art at the time of the invention suggested or motivated a skilled artisan to use the particular low dose combination claimed by Appellants.

As discussed above, Plunkett discloses a myriad of estrogens and progestins that can be combined to treat numerous disorders. Of the thousands of possibilities with the disclosed genus, Plunkett discloses of 0.600 mg CEE and 2.5 mg of MPA as the preferred doses. (Tables 1A and 1B). Appellants' claims require a dose of about 0.3 to about 0.45 mg CEE and a dose of about 1.5 mg MPA. When the claimed invention is compared with Plunkett's preferred dosage (which is the closest disclosed species), Plunkett's regimen recites a dose of CEE that is between 33% and 100% higher than Appellants' regimen, and a dose of MPA that is 66% higher than Appellants' regimen. Moreover, it is well established that a species is patentable within a prior art genus absent a motivation for one skilled in the art to make the claimed invention. *See, e.g., In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994); and *In re Jones*, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). Nothing in Plunkett, including the closest disclosed species, teaches or suggests the low dose combination claimed by the Appellants.

Furthermore, as described by Dr. Lobo, those skilled in the art considered the commercial regimen of 0.625 mg CEE plus 2.5 mg MPA as the standard dosage of estrogen and MPA necessary to relieve the symptoms of menopause, including hot flushes and bone loss. (Lobo Declaration ¶ 8). Indeed, Dr. Lobo states that the results of the study set forth on page 9 of the specification, showing that the lower doses of CEE and MPA reduced the number and severity of hot flushes, were contrary to what would have been expected by those skilled in the art. (Lobo Declaration ¶ 6). Accordingly, the teachings of the prior art and the knowledge generally available in the art would not have suggested to those skilled in the art that the use of 1.5 mg MPA in combination with about 0.3 mg to about 0.45 mg CEE would have been reasonably successful in providing relief of vasomotor symptoms of menopause.

Moreover, even assuming *arguendo* that it would have been *obvious to try* Appellants' low dose combination, as the Examiner has suggested, this is not the appropriate standard to use in reaching an obviousness determination. *See In re Fine*, 837 F.2d 1071, 1075-76, 5 U.S.P.Q.2d at 1598-1600 (Fed. Cir. 1988). The Federal Circuit in *In re Fine* stated that:

> The PTO has the burden under section 103 to establish a prima facie case of obviousness. It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available

> to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. This it has not done . . . .
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> * * *
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> Instead, the Examiner relies on hindsight in reaching his obviousness determination . . . . One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

Id.

It is respectfully submitted that the Examiner offers no evidence, but only conclusory, hindsight speculation in support of her position of obviousness. However, when applying 35 U.S.C. §103, the prior art reference must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. *See Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); and MPEP §2141. In this instance, the unrefuted evidence provided by the Appellants shows that optimization of the dosage amounts was not obvious to one of skill in the art because the selected Plunkett regimen was accepted as the minimum dosage necessary to provide relief from hot flushes. (*See* Lobo Declaration ¶ 8).

c) Appellants Have Demonstrated Unexpected Results Over the Closest Prior Art

The Appellants respectfully submit that even assuming *arguendo* that the Examiner had established a *prima facie* case of obviousness, the evidence provided by the Appellants clearly rebuts the *prima facie* case by showing that the claimed invention possesses unexpectedly improved properties. The Appellants have provided data demonstrating unexpected results over the closest prior art. Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. *See In re Boesch*, 617 F.2d 272, 205 U.S.P.Q. 215 (C.C.P.A. 1980). *See also* MPEP §716.02(d)-§716.02(e).

The pending application provides data setting forth some of the results of a double blind clinical study of postmenopausal women using combinations of PREMARIN (conjugated estrogens tablets, USP) plus MPA, or placebo. (*See* Pages 8-9). The results of the study reported on page 9 of the specification surprisingly and

unexpectedly demonstrated that providing a much lower daily dosage of 1.5 mg MPA in combination with 0.45 or 0.30 mg CEE reduced the number and severity of hot flushes to essentially the same extent as the standard, commercially available dose combination of 0.625 mg CEE and 2.5 mg MPA. (Second Lobo Declaration ¶6).

As explained by Dr. Lobo, for the past 20 years, the dosage of 0.625 mg CEE has been accepted as the minimum dosage of estrogen necessary to relieve the symptoms of menopause, including vasomotor symptoms. Furthermore, the dosage of 2.5 mg of MPA has been recognized as the minimum amount needed to oppose 0.625 mg CEE and to protect the endometrium. This daily dosage combination of 0.625 mg CEE plus 2.5 mg MPA has been the most commonly prescribed combination estrogen-progestin hormone replacement therapy regimen in the United States. (*See* Second Lobo Declaration ¶ 2).

The closest species disclosed by Plunkett, which is 0.600 mg CEE plus 2.5 mg MPA, is equivalent to the commonly prescribed higher dosage regimen, 0.625 mg CEE plus 2.5 mg MPA. Although there is a slight variation in the dosage of CEE, one skilled in the art would consider a daily dosage of 0.625 mg CEE to be clinically equivalent to a dosage of 0.600 mg CEE for the purposes of treating vasomotor symptoms. (*See* Second Lobo Declaration ¶ 3). Because the commonly prescribed regimen (0.625 mg CEE in combination with 2.5 mg MPA) and the closest species disclosed in Plunkett are equivalent, Appellant's demonstration of unexpected results over the commonly prescribed regimen is equally applicable to show unexpected results over the Plunkett regimen.

As set forth in Dr. Lobo's first declaration, he worked with other scientists and doctors to develop the clinical protocol for the study reported on page 9 of the specification, referred to as the Women's Health, Osteoporosis, Progestin, Estrogen study ("H.O.P.E. study"), and was involved as a trial investigator. (Lobo Declaration ¶ 9). In the H.O.P.E. study, patients received continuous and uninterrupted treatment for 13 to 26 cycles, consisting of the following eight regimens administered daily: (1) 0.625 mg CEE; (2) 0.45 mg CEE; (3) 0.3 mg CEE; (4) 0.625 mg CEE plus 2.5 mg MPA ("PREMPRO"); (5) 0.45 mg CEE plus 2.5 mg MPA; (6) 0.45 mg CEE plus 1.5 mg MPA; (7) 0.3 mg CEE plus 1.5 mg MPA; and (8) a placebo. (Lobo Declaration ¶ 11).

The results from the H.O.P.E. study surprisingly and unexpectedly demonstrated that all doses of CEE and MPA reduced the number and severity of hot flushes experienced by the women in this study compared with women taking placebo. (Lobo Declaration ¶ 14). Specifically, it was unexpected that providing a daily dosage of 1.5 mg MPA in combination with the lower doses, 0.45 or 0.30 mg, CEE, rapidly reduced the number and severity of hot flushes to the same extent as the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA. (Lobo Declaration ¶ 14).

Moreover, the H.O.P.E. study further unexpectedly showed an additive effect of MPA at low doses. Prior studies using various dosages of CEE had demonstrated that MPA had no additive effect in relieving vasomotor symptoms, and the presence of MPA was thought to be merely prophylactic (Lobo Declaration ¶ 15). That is, it was thought that CEE plus MPA was no more effective in relieving hot flushes as compared to CEE alone. However, the H.O.P.E. study surprisingly demonstrated that the particular low dose of 1.5 mg MPA may contribute vasomotor relief in combination with the lower dosages of 0.3 or 0.45 mg CEE. Thus, Appellants' invention unexpectedly contradicts the accepted view by demonstrating the additive effect of MPA at low dosages.

The Appellants respectfully disagree with the Examiner's position that the data provided on page 9 of the specification does not constitute unexpected results because the data presented shows similar efficacy in treating vasomotor symptoms between the standard commercially available regimen, 0.625 mg CEE/2.5 mg MPA, and the lower dosage regimens claimed herein, 0.45 mg CEE/1.5 mg MPA and 0.30 mg CEE/1.5 mg MPA. (Office Action, p. 4). The Examiner further noted that some of the data points overlap in both number and severity of hot flushes. However, these similar therapeutic results that are reported on page 9 of the specification are precisely what was unexpected to one skilled in the art.

As explained in Dr. Lobo's declarations, prior to the Appellants' invention, one skilled in the art would expect that a low dose regimen would have *some effect* in reducing the number and severity of hot flushes. However, a skilled artisan would have expected *far less of an effect* than the standard dose of 0.625 mg CEE plus 2.5 mg MPA. (Lobo Declaration ¶ 12 and Second Lobo Declaration ¶ 6). In fact, Dr. Lobo and others skilled in the art doubted that a study of low dose regimens was

worth the economic effort. (Lobo Declaration ¶ 12). Despite the presumption that the standard regimen was the minimum effective dose, Appellants demonstrated that the low dose regimen was *equally effective* at relieving hot flushes. (Lobo Declaration ¶ 14 and Second Lobo Declaration ¶ 5).

Appellants also respectfully disagree with the Examiner's assertions that because the lower dosage combinations yielded similar therapeutic results as with the standard commercially available combination, the Appellants have confirmed the teachings of Plunkett that the entire range is effective in treating hot flushes. Appellants are required to compare their claimed invention with the closest species disclosed in the prior art. *See* MPEP §2144.08(II)(A)(2) ("the closest disclosed species or subgenus in the prior art reference should be identified and compared to that claimed."). In Plunkett, the closest species is 0.600 mg CEE in combination with 1.5 mg MPA. Applicants have made such a comparison and have demonstrated unexpected results over Plunkett. Appellants respectfully submit that contrary to the Examiner's position, they do not confirm the efficacy of the entire Plunkett genus, but rather only demonstrate the efficacy of the claimed low dose regimen.

The Examiner states that Dr. Lobo's declaration does not clearly and convincingly show unexpected benefits residing in the claimed dosage regimen. Appellants respectfully disagree. Dr. Lobo's statements are not only based on cited references, but are also based on his knowledge as a practicing physician in the field. Dr. Lobo has extensive experience in treating women for symptoms of menopause, including hot flushes, and has knowledge of what other skilled in the art prescribed for their patients. Thus, the evidence provided by Dr. Lobo should be given a great deal of weight in the determination of patentability of the pending claims.

Conclusion of Argument

It is respectfully submitted that the Examiner has not made a *prima facie* case of obviousness because Plunkett, the sole reference cited against the Appellants' claims, does not teach or suggest the selection of about 1.5 mg MPA in combination with about 0.3 to about 0.45 mg CEE, as recited in the appealed claims. Furthermore, the unrefuted evidence provided in the specification and by Dr. Lobo convincingly demonstrates the unexpected results obtained with Appellants' invention.

Accordingly, Appellants respectfully submit that the rejection of the appealed claims should be reversed.

Fee Authorization

The Commissioner is authorized to charge the fee for this appeal brief of $340.00 as set forth in 37 C.F.R. §1.17(c) and any other fees that may be necessary for the consideration of this appeal brief to Deposit Account No. 11-0600.

Respectfully submitted,

Dated: October 19, 2004

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Appendix A

7. A method of treating or inhibiting vasomotor symptoms in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a combination of conjugated estrogens, USP and a daily dosage of about 1.5 mg of medroxyprogesterone acetate, wherein the daily dosage of conjugated equine estrogens is between about 0.45 mg and about 0.3 mg.

11. The method according to claim 7, wherein the daily dosage of conjugated equine estrogens, USP is about 0.3 mg.

12. The method according to claim 7, wherein the vasomotor symptom is hot flushes.

69. The method according to claim 7, wherein the daily dosage of conjugated equine estrogens, USP is about 0.45 mg.